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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,131	06/08/2001	Guofan Hong	Lee113	1143
7590		10/15/2003	EXAMINER	
Marlana Titus		CHUNDURU, SURYAPRABHA		
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Suite 1000		PAPER NUMBER		
3415 Brookeville Road		1637		
Brookeville, MD 20833		2		

DATE MAILED: 10/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/878,131

Applicant(s)

HONG ET AL.

Examiner

Suryaprabha Chunduru

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 and 18-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 18-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action (Paper No. 20) filed on June 2, 2003 has been entered and considered.
2. Claims 1-11, 18-35 are pending.

Response to arguments

3. Applicants' response to the office action (Paper No. 20) is fully considered and found persuasive.
4. With reference to the rejection made in the previous office action under 35 USC 102(b) and 102(e), Applicants' arguments are fully considered and found persuasive. Applicant's arguments regarding the Hong et al. references have been considered, however, the particular argument that the references do not teach cycle primer extension is found not persuasive because in all the references of Hong et al. polymerase mediated primer extension is done by repeated primer extension under low temperature conditions. However the rejection is withdrawn herein in view of the amendment and arguments and new grounds of rejection.
5. With reference to the rejection made in the previous office action under nonstatutory double patenting, the rejection is maintained herein since applicants did not address this rejection nor submitted a terminal disclaimer.

New Grounds of rejections

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurn et al. (USPN. 6,200,757) and in view of Mian et al. (USPN. 5,686,271).

Kurn et al. teach a method of claim 1, for extending an oligonucleotide primer or a pair of primers using an enzymatic cycle primer extension (see column 6, lines 21-55, column 22, lines 44-67, column 23, lines 1-19), (with regard to claim 5) at temperatures between about 45 C and about 65 C (with regard to claims 1 and 3) and a melting temperature of about 70 C (see column 19, lines 41-54, column 23, lines 2-19);

comprising the step of mixing a template DNA with a primer or a pair of primers and a natural or modified DNA polymerase (see column 6, lines 59-67, column 7, lines 1-5), wherein (with reference to claims 1, and 4) the DNA polymerase is selected from the group consisting of *Bacillus stearothermophilus* (Bst DNA polymerase), Pfu DNA polymerase, Vent and Tli DNA polymerase (see column 14, lines 30-45) which has proofreading 3'-5' exonuclease activity during primer extension over a template, such that the DNA polymerase functions to excise mismatched nucleotides from the 3' terminus of the DNA (see column 14, lines 46-62) under

conditions that the cycle reaction temperature of about 37 C, so that the DNA polymerase repeatedly extends the primer(s) to produce a sequence-specific product (see column 19, lines 16-56).

With regard to claim 6, Kurn et al. teach amplification with a forward and a reverse primer (see column 33, lines 1-7) and

With regard to claim 7, the lengths of each primer differs (see column 33, lines 1-7).

However Kurn et al. did not teach use of glycerol, ethylene glycol or a mixture of glycerol and ethylene glycol of concentration between about 10% and about 20% (v/v).

Mian et al. teach a method of claims 1-2, for cycle primer extension wherein the amplification reaction comprises 5% glycerol, and 5% ethylene glycol (see column 16, lines 52-63). Mian et al. also teach that the method uses denaturants to reduce the melting temperatures of target nucleic acids having higher G+C content (see column 11, 55-67, column 12, lines 1-25).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of cycle primer extension at low temperatures as taught by Kurn et al. with the teachings as taught by Mian et al. to develop an improved method for cycle primer extension because Mian et al. states that 'it is beneficial to carry out duplex dissociation at a temperature near the T_m of the duplex, the dissociation should occur at a temperature that does not destabilize the polymerase enzyme used for primer extension. It is preferable to use agents that lower the T_m . The agents include lower alkyl alcohols, urea, formamide and other hydrogen bond competitors (see column 11, lines 56-67, column 12, lines 1-25). An ordinary practitioner would have been motivated to modify the method of Kurn et al. by incorporating the parameters or limitations (adding glycerol and ethylene glycol) as taught by

Mian et al., since inclusion of said limitations would improve specificity of polymerase mediated primer extension and result in an improved method for cycle primer extension.

B. Claims 8-11, 18-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong et al. (USPN. 6,165,765) and in view of Mian et al. (USPN. 5,686,271).

Hong et al. teach a method of claims 8-9, 22-23, 28-31, for extending an oligonucleotide primer using an enzymatic cycle primer extension reaction at annealing temperatures between 45 C and about 60 C and melting temperature of about 70 C (see column 8, lines 5-7) comprising (i) mixing a template with a primer and extending the primer using a modified or unmodified DNA polymerase which has an ability to reduce selective discrimination against incorporation of fluorescent dye-labeled ddNTPs, ddCTP and ddATP, in the presence of the dNTPs or their analogs and fluorescent ddNTPS (see column 10, lines 42-57, column 15, lines 50-67, column 16, lines 1-16).

With regard to claims 9, 11, 22, (ii) DNA polymerase selected from *Bacillus stearothermophilus*, *Bacillus caldotenax*, or *Bacillus caldolyticus* (see column 6, lines 48-64); method also comprises nucleotide analogs, such as ddCTP, ddATP which reduce innate selective discrimination against the incorporation of fluorescent dye-labeled ddNTPs (see column 6, lines 48-64) (with regard to claim 8).

With reference to the instant claims 24-27, 32-35, Hong et al. teach that the method comprises DNA polymerase having homology (99-100%) to the instant claimed SEQ ID Nos. 1-4 (see sequence alignment).

With reference to the instant claim 29, extension of a primer of different length in the presence of ddNTS (see column 17, lines 1-23).

However Hong et al. did not teach use of glycerol, ethylene glycol or a mixture of glycerol and ethylene glycol of concentration between about 10% and about 20% (v/v).

Mian et al. teach a method of claims 1-2, for cycle primer extension wherein the amplification reaction comprises 5% glycerol, and 5% ethylene glycol (see column 16, lines 52-63). Mian et al. also teach that the method uses denaturants to reduce the melting temperatures of target nucleic acids having higher G+C content (see column 11, 55-67, column 12, lines 1-25).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of cycle primer extension at low temperatures as taught by Hong et al. with the teachings as taught by Mian et al. to develop an improved method for sequencing a target nucleic acid because Mian et al. states that 'it is beneficial to carry out duplex dissociation at a temperature near the T_m of the duplex, the dissociation should occur at a temperature that does not destabilize the polymerase enzyme used for primer extension. It is preferable to use agents that lower the T_m . The agents include lower alkyl alcohols, urea, formamide and other hydrogen bond competitors (see column 11, lines 56-67, column 12, lines 1-25). An ordinary practitioner would have been motivated to modify the method of Hong et al. by incorporating the parameters or limitations (adding glycerol and ethylene glycol) as taught by Mian et al., since inclusion of said limitations would improve specificity of polymerase mediated primer extension and result in an improved method for sequencing using cycle primer extension.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the

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examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

^{SPC}
Suryaprabha Chunduru
October 10, 2003


JEFFREY FREDMAN
PRIMARY EXAMINER